# Studies on Local Anesthetics XXVI

## Influence of the Lateral Side Chain on the Anesthetic Activity of Substituted Basic Acetanilides

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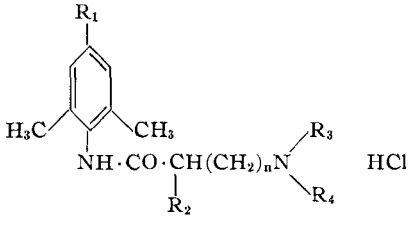
**A series of twenty-two substituted basic acetanilides, in which the chemical structure of the acyl substituents and amino groups were modified, has been prepared. At the same time the synthesis of ω-diethylaminothioaceto-2,6-xylidide and -2,4,6-mesidide has been reported. The anesthetic activity of these compounds as determined by surface and infiltration methods has been reported and the results of toxicity tests have been summarized.**

THE METHYLATED analog of lidocaine,[1] ω-diethylaminoaceto-2,4,6-mesidide, already described by Löfgren in 1946 (1), has recently awakened the interest of other research groups (2–7). The advantageous results of the pharmacological tests and clinical trials of this substance as well as, under certain circumstances, its better accessibility have led to its introduction into practical medicine under the name of Mesokain (8).

These facts indicated the desirability of preparing a series of basic acetanilides of general formula I, in which the influence of the structural



$R_1$ = H, $CH_3$
$R_2$ = H, $CH_3$–$C_3H_7$
$R_3$, $R_4$ = H, alkyl, alkylene, etc.
n = 0, 1

changes of the lateral side chain on the local anesthetic activity might be investigated. These studies included the influence on activity effected by ramifying substitutions around the acyl radical and chemical modifications of the amino group. Simultaneously, the thioanalogs of lidocaine and Mesokain[2] were prepared. The preparation and pharmacological evaluation of the substances described in this study are the continuation of previous papers from this laboratory on substituted basic acetanilides (7, 11) and thioderivatives of the series of substituted ω-aminoacetophenones (12).

The compounds were prepared according to the method previously used (7, 11), i.e., by the reaction of the corresponding halo-acetanilides with diethylamine. The thioacetanilides were obtained by action of phosphorus pentasulfide on corresponding acetanilides.

### EXPERIMENTAL[3]

**Diethylaminoacetomesidides (I; S 352–S 395).**—These were prepared in the majority of cases according to the method previously used (7, 11) by the reaction of the corresponding chloroacetanilides with the diethylamine in boiling anhydrous benzene.

In the cases in which the reactivity of the starting products was reduced by the steric factor resulting from α-alkylation, the reaction was carried out in autoclave at 140–160° (S 383, S 388, S 390–S 392). For a similar reason the more reactive bromo derivatives were used as the starting halo-acetanilide intermediate.

The β-diethylaminopropiono-2,4,6-mesidide (S 395) was prepared at laboratory temperature (forty-eight days) in order to avoid the formation of an acrylomesidide by-product.

The ω-(4-carbethoxypiperazino-1)-acetomesidide (S 385) was prepared by the reaction of equivalents of chloroacetomesidide and 1-carbethoxypiperazine in presence of sodium bicarbonate in boiling ethanol.

The starting halo-aceto-2,4,6-mesidides were prepared by the reaction of chlorides of corresponding halo-aliphatic acids with mesidine in acetic acid over sodium acetate (1).

**Thioacetanilides (S 322 and S 323).**—These were prepared by the reaction of the corresponding acetanilides with the phosphorus pentasulfide in anhydrous pyridine (13).

The final substances were converted to the hydrochlorides and isolated as such. These were precipitated from anhydrous ether or benzene solution of

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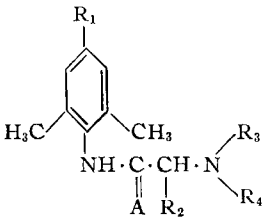
[1] The trade name of lidocaine is Xylocaine (Astra).
[2] After having finished the experimental part of this study we discovered the existence of the studies of Löfgren's group (9, 10) who simultaneously with us prepared five derivatives (S 322, S 323, S 352, S 357, and S 374).
[3] All melting points were determined on the Kofler block and are corrected. Microanalyses were carried out by Mrs. Kleinová-Parolková.

TABLE I.—SUBSTITUTED BASIC ACETANILIDE AND THIOACETANILIDE HYDROCHLORIDES



| No. | $R_1$ | A | $R_2$ | $R_3$ | $R_4$ | M. p., °C. | Solubility, $H_2O$, % | N, % Calcd. | N, % Found | Cl, % Calcd. | Cl, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| S 322 | H | S | H | $C_2H_5$ | $C_2H_5$ | 162[a] | ... | 9.77 | 9.88 | ... | ... |
| S 323 | $CH_3$ | S | H | $C_2H_5$ | $C_2H_5$ | 160[b] | ... | 9.31 | 9.38 | ... | ... |
| S 352 | $CH_3$ | O | H | $C_4H_9$ | H | 247[c] | 1.7 | 9.84 | 9.75 | ... | ... |
| S 354 | $CH_3$ | O | H | $C_6H_{13}$ | H | 199 | 0.45 | 8.95 | 8.86 | 11.33 | 11.30 |
| S 357 | $CH_3$ | O | H | $C_6H_{11}$ | H | 254[d] | 2 | 9.01 | 8.98 | ... | ... |
| S 359 | $CH_3$ | O | H | $C_6H_5CH_2$ | H | 205 | 0.9 | 8.79 | 8.72 | 11.12 | 10.88 |
| S 371 | $CH_3$ | O | H | $C_4H_9$ | $C_4H_9$ | 126 | 3.4 | 8.22 | 8.25 | 10.40 | 10.38 |
| S 381 | $CH_3$ | O | H | $C_6H_5$ | $C_2H_5$ | 163 | 0.09 | 8.42 | 8.23 | 10.65 | 10.56 |
| S 384 | $CH_3$ | O | H | $CH_2CH_2CH_2CH_2$ | | 213–214 | (40–50) | 9.91 | 9.90 | 12.54 | 12.57 |
| S 374 | $CH_3$ | O | H | $CH_2CH_2CH_2CH_2CH_2$ | | 196[e] | (38) | 9.44 | 9.35 | ... | ... |
| S 375 | $CH_3$ | O | H | $CH(CH_3)\cdot CH_2CH_2CH_2CH_2$ | | 188 | (40–50) | 9.01 | 9.01 | 11.41 | 11.47 |
| S 376 | $CH_3$ | O | H | $CH_2CH(CH_3)\cdot CH_2CH_2CH_2$ | | 104 | (5) | 9.01 | 9.00 | 11.41 | 11.42 |
| S 377 | $CH_3$ | O | H | $CH_2CH_2CH(CH_3)\cdot CH_2CH_2$ | | 217–219 | (>50) | 9.01 | 8.82 | 11.41 | 11.32 |
| S 383 | $CH_3$ | O | H | $CH(CH_3)\cdot CH_2CH_2CH_2CH(CH_3)$ | | 261 | 4.7 | 8.60 | 8.61 | 10.89 | 10.78 |
| S 388 | $CH_3$ | O | H | $CH(CH_3)\cdot CH_2CH(CH_3)\cdot CH_2CH(CH_3)$ | | 175 | 4.3 | 8.27 | 8.15 | 10.46 | 10.45 |
| S 378 | $CH_3$ | O | H | $CH_2CH_2O\cdot CH_2CH_2$ | | 250 | (12) | 9.38 | 9.29 | 11.87 | 11.74 |
| S 379 | $CH_3$ | O | H | $CH_2CH_2S\cdot CH_2CH_2$ | | 225 | 6.4 | 8.90 | 8.67 | 10.90 | 11.17 |
| S 385 | $CH_3$ | O | H | $CH_2CH_2N(COO\cdot C_2H_5)\cdot CH_2CH_2$ | | 132 | 6 | 11.39 | 11.30 | 9.61 | 9.45 |
| S 390 | $CH_3$ | O | $CH_3$ | $C_2H_5$ | $C_2H_5$ | 212 | (>50) | 9.37 | 9.29 | 11.86 | 11.90 |
| S 391 | $CH_3$ | O | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | 216–217 | 16 | 8.95 | 8.89 | 11.34 | 11.47 |
| S 392 | $CH_3$ | O | $C_3H_7$ | $C_2H_5$ | $C_2H_5$ | 175 | (2–5) | 8.57 | 8.54 | 10.85 | 10.90 |
| S 395 | $CH_3$ | | $CO\cdot CH_2CH_2N(C_2H_5)_2$[f] | | | 163 | (>50) | 9.37 | 9.28 | 11.86 | 11.05 |

[a] Lüning (9) m.p. 106.5–107°. [b] Lüning (9) m. p. 121°. [c] Literature (10) m. p. 237–238°. [d] Literature (10) m. p. 261–262°. [e] Literature (10) m. p. 197–199°. [f] Compound mentioned in patent literature (16) but constants are not given.

bases by addition of ethereal hydrogen chloride. The yields were generally good (in preparation of the bases, 50–90%).

The melting points and analyses of the substances prepared are included in Table I.

The solubilities of the hydrochlorides were determined by the mercurimetric titration of chloride ion in solutions saturated at room temperature. The results are given in Table I. The values in parentheses are the results of preliminary experiments in test tubes.

## PHARMACOLOGY

The relative activity of the compounds in surface anesthesia (rabbit cornea, 0.01*M* cocaine as standard) and infiltration anesthesia (intradermal application to guinea pigs, 0.02*M* procaine as standard) was calculated from the molar concentration experimentally found to give the same effect as the standard. The method has been described in detail by Vrba and Sekera (14).

The toxicity was studied according to Kärber (15) by determining the $LD_{50}$ in white mice (strain H) by subcutaneous application.

The results are given in Table II.

## DISCUSSION AND SUMMARY

Twenty-two derivatives of the lidocaine series were prepared and tested for local anesthetic activities and toxicity.

The following correlations between the anesthetic activity, acute toxicity, and chemical structure of the compounds studied can be made:

1. Ramifications of the acyl chain in general appear to accentuate the anesthetic action in surface anesthesia as in infiltration anesthesia; this effect increases with the prolongation of the lateral side chain

TABLE II.—PHARMACOLOGICAL PROPERTIES

| Substance | Relative Activity — Surface Anesthesia | Relative Activity — Infiltration Anesthesia | $LD_{50}$ s. c., mg./Kg. |
|---|---|---|---|
| S 322 | 0.17 | 0.77 | 820 |
| S 323 | 0.05 | 0.66 | >14,000 |
| S 352 | 0.62 | 2.6 | 270 |
| S 354 | 4.9 | 1.2 | 280 |
| S 357 | 2.7 | 8.3 | 170 |
| S 359 | 2.2 | 4.1 | 630 |
| S 371 | 9.3 | 5.1 | >4,500 |
| S 381 | Sparingly soluble[a] | Sparingly soluble[a] | Sparingly soluble[b] |
| S 384 | 0.45 | 2.1 | 540 |
| S 374 | 0.43 | 1.5 | 320 |
| S 375 | 0.6 | 4 | 240 |
| S 376 | 2.6 | 8.4 | 580 |
| S 377 | 2.8 | 5.5 | 570 |
| S 383 | 3.3 | 3.4 | 480 |
| S 388 | 3 | 4.4 | 940 |
| S 378 | (0.2–0.3) | 3.1 | 660 |
| S 379 | Sparingly soluble[c] | Sparingly soluble[c] | >2,300 |
| S 385 | 0.07 | 1.1 | 710 |
| S 390 | 0.76 | 3.6 | 370 |
| S 391 | 1.2 | 4 | 250 |
| S 392 | 9.3 | 7.7 | 135 |
| S 395 | 0.59 | 1.2 | 390 |
| S 202 (lidocaine) | 0.24 | 1.4 | 370 |
| S 203 (Mesokain) | 1 | 2.5 | 350 |
| Cocaine | 1 | 3.6 | 125 |
| Procaine | 0.15 | 1 | 630 |

[a] No action after application of 0.00303 *M* solution. [b] $LD_0 \geq 90$ (saturated solution). [c] No action after application of 0.2*M* solution.

(S 390–S 392). The prolongation of the nonramified chain, if it is possible to judge from a single example (S 395), does not seem to offer any advantage.

2. The N-monosubstituted derivatives (S 352, S 354, S 357, and S 359) were seen to be generally more active than the model substance, Mesokain (S 203). It must be noted, however, that they are also more toxic, with the exception of the benzyl derivative (S 359) which seems to be the most advantageous of this subgroup.

3. The only aliphatic substituted derivative, dibutylaminoacetomesidide (S 371), is almost ten times more active in surface anesthesia and two times more active in infiltration anesthesia than Mesokain, and more than ten times less toxic than this model substance.

4. Replacing of the diethylamino group in the Mesokain molecule by a cycloaliphatic amine was seen to be advantageous and therefore received greater attention.

Replacing by morpholine (S 378), carbethoxypiperazine (S 385), and especially by thiomorpholine (S 379) produces, indeed, a lowering of toxicity but in general also a parallel fall in activity.

Replacing by pyrrolidine (S 384) lowers toxicity and activity. Replacing by nonsubstituted piperidine (S 374) is also not too advantageous; however, in the series of methylpiperidine derivatives fall several substances having the best activity-toxicity ratio of the entire series of compounds described in this paper.

Among the monomethylpiperidino derivatives the most advantageous is the derivative of β-picoline (S 376), which is more than two times more active in surface anesthesia and three times more active in infiltration anesthesia than Mesokain, and at the same time nearly two times less toxic. The derivatives of 2,6-lupetidine (S 383) and 2,4,6-copellidine (S 388) were found to be even more interesting, being approximately three times more active in surface anesthesia and also more active in infiltration anesthesia than Mesokain, and simultaneously less toxic. The favorable activity-toxicity ratio of all these substances stand out also in comparison with cocaine and procaine.

5. Substituting sulfur for oxygen in the series studied was seen to be much less favorable than in theFalicaine series (12). Thio-lidocaine (S 322) as well as thio-Mesokain (S 323) were, indeed, found to be less toxic than the corresponding oxygenated substances, but also were less active. This effect is even more pronounced in the case of substitution of sulfur for the oxygen of morpholine in the lateral side chain of the substance S 378: the thiomorpholino derivative (S 379) is only very slightly toxic but practically without anesthetic action.

A more thorough study of the most promising substances is under way. It will be published elsewhere along with the results of the study of the relations between the anesthetic activities of the substances described in this paper with their physicochemical properties such as surface activity, liposolubility, ability to coagulate colloids, basicity, etc.

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